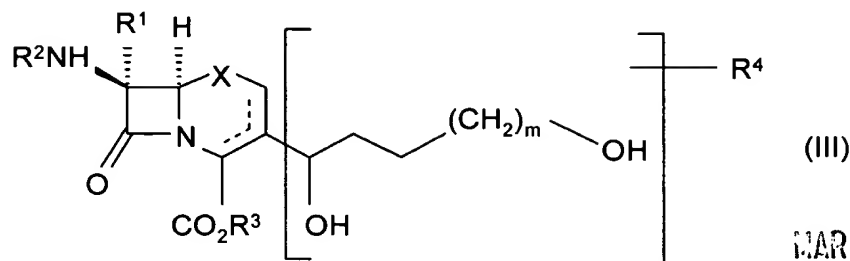


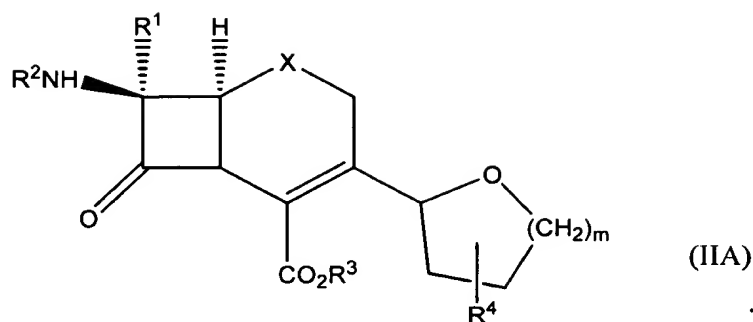
comprising cyclizing a compound of formula (III):



MAR 11 2004

wherein in formulae (II) and (III), R<sup>1</sup> is hydrogen, methoxy or formamido; R<sup>2</sup> is an acyl group; CO<sub>2</sub>R<sup>3</sup> is CO<sub>2</sub>H, a carboxylate salt or a carboxy group protected by benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus- containing group, an oxime radical of formula -N=CHR<sup>7</sup> where R<sup>7</sup> is aryl or heterocyclic, or an *in vivo* hydrolysable ester group; R<sup>4</sup> represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO<sub>2</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub> (where R is hydrogen or C<sub>1-6</sub> alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO<sub>2</sub>, O, or CH<sub>2</sub>; and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s) R<sup>4</sup> when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain, and, when R<sup>3</sup> is hydrogen optionally forming the carboxylate salt of said compound of formula III.

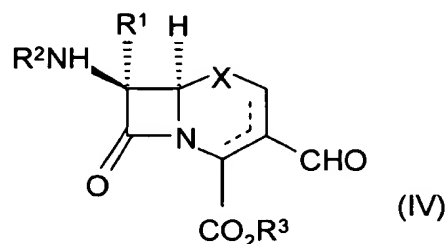
2. (PREVIOUSLY AMENDED) The process according to claim 1 wherein the compound of formula (II) is a 3-cephem of formula (IIA) or a pharmaceutically acceptable salt or pharmaceutically acceptable *in vivo* hydrolyzable ester thereof:



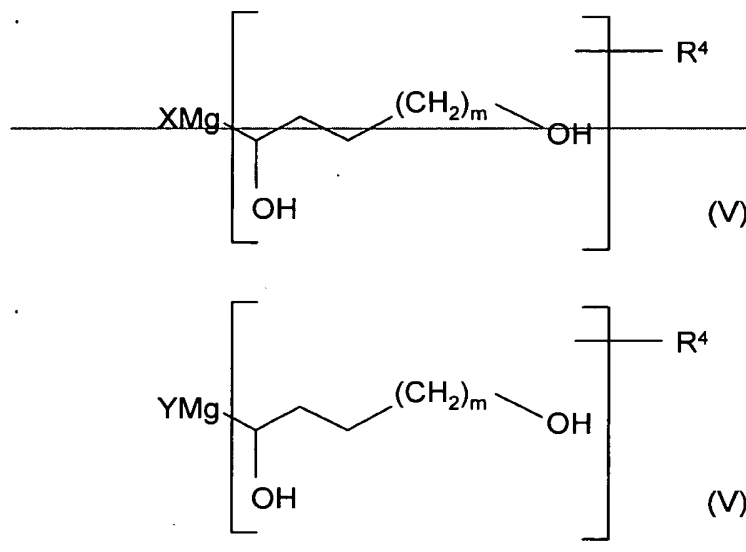
3. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein X is S, O, or CH<sub>2</sub>.
4. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein the cyclic ether at the 3-position of the cephalosporin nucleus in formulae (II) and (IIA) is unsubstituted.
5. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein m is 1, so that the cyclic ether at the 3-position in formulae (II) and (IIA) is a tetrahydrofuranyl system.
6. (PREVIOUSLY AMENDED) The process according to claim 5 wherein the cyclic ether at the 3-position in formulae (II) and (IIA) is an (S)-tetrahydrofuran-2-yl ring system.
7. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein in formula (III) when m is 1 the 1, 4-dihydroxylbut-1-yl side chain is the less polar diastereoisomeric form.
8. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein the cyclization reaction of the process of the invention is carried out by treatment of the compounds (III) with an acid catalyst.
9. (PREVIOUSLY AMENDED) The process according to claim 1 or 2 wherein the cyclization reaction is carried out by treatment of the compounds (III) with an acylating

agent.

10. (CURRENTLY AMENDED) The process according to claim 1 or 2 wherein the compound of formula (III) is prepared by reacting a compound of formula (IV):

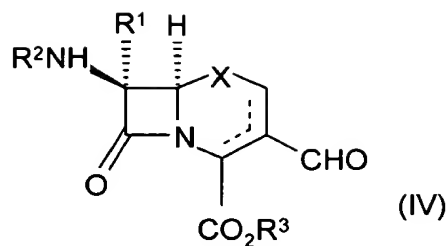


with a compound of formula (V):

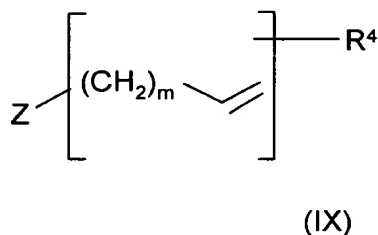


where  $R^4$  and  $m$  are as defined with respect to formula (III), and  $X$  is  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , or  $CH_2$  and  $X$   $Y$  is ~~are the same or different~~ halogen, and the dotted line in formula (IV) indicates that the compound (IV) may be a 2- or 3- cephem system.

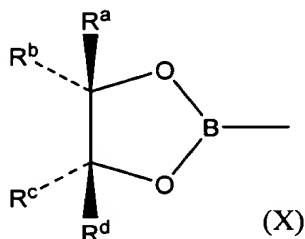
11. (CURRENTLY AMENDED) The process according to claim 1 or 2, wherein the compound of formula III is prepared by coupling a compound of formula (IV)



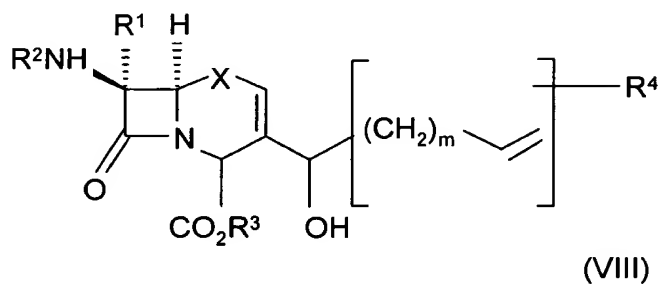
(as defined in claim 10) with an organometallic reagent or a compound having the structure (IX)



wherein Z is boronate group (X)



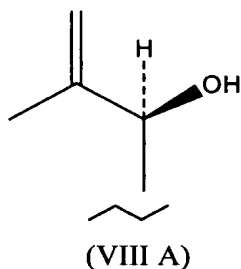
wherein  $R^a$ ,  $R^b$ ,  $R^c$  and  $R^d$  are independently selected from hydrogen, alkyl and protected carboxy to form a compound of formula (VIII):



and wherein said compound of formula VIII is then hydroxylated to form a compound of formula III, where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $m$ , and  $X$  are as defined with respect to

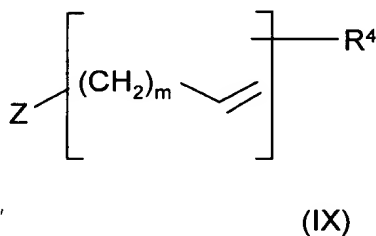
formula (III).

12. (PREVIOUSLY AMENDED) The process according to claim 11 wherein the compound of formula (VIII) has the configuration shown in (VIII A):



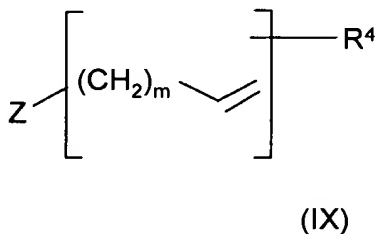
13. (PREVIOUSLY AMENDED) The process according to claim 12 wherein the compound of formula (IV) is formed into a compound of formula (VIII) by reaction with an organometallic reagent.

14. (PREVIOUSLY AMENDED) The process according to claim 13 wherein the organometallic reagent is a compound of formula (IX):



where  $m$  and  $R^4$  are as defined in formula (VIII), and  $Z$  is  $YMg$  where  $Y$  is a halogen.

15. (CURRENTLY AMENDED) The process according to claim 11 wherein the compound of formula (VIII) is prepared stereospecifically from a compound of formula (IV) by the use of a compound (IX):

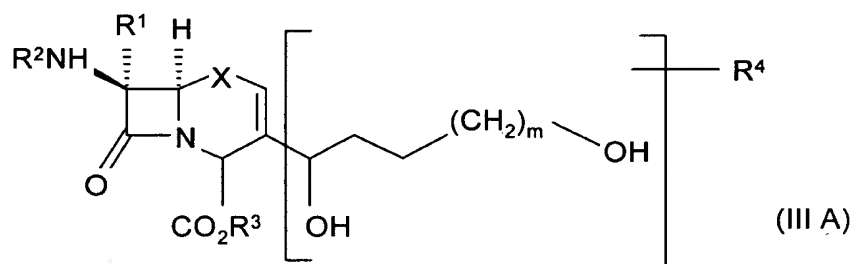


in which Z is a chirally inducing group which leads to preferential formation of a desired configuration of the hydroxyl group in the compound (VIII).

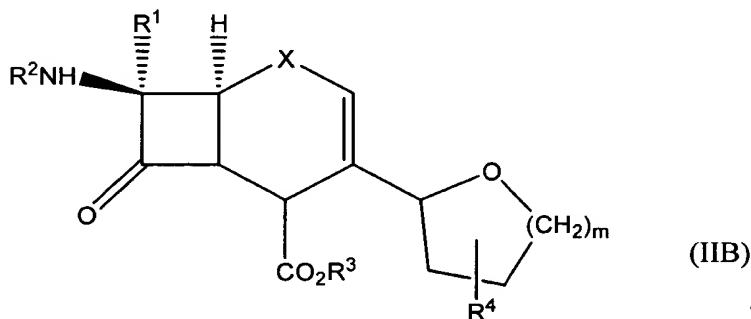
16. (CANCELLED)

17. (CURRENTLY AMENDED) The process according to claim 16 wherein group (X) is a pinacol boronate group.

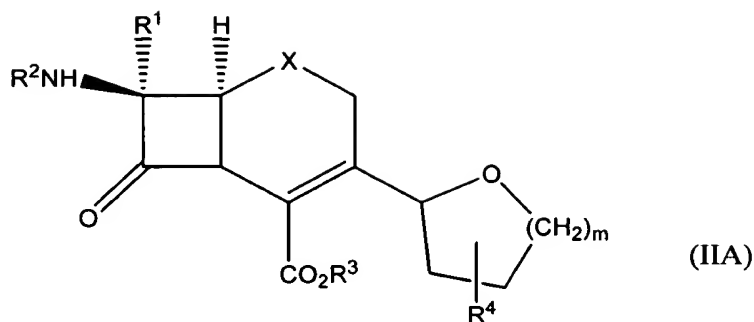
18. (CURRENTLY AMENDED) The process according to claim 10 wherein the compound (IV) is alkylated with a compound of formula (V) to form a compound of formula (III), which is then hydroxylated to form a 2-ephem compound of formula (IIIA):



which is then cyclized to form a 2-ephem compound of formula (IIB):

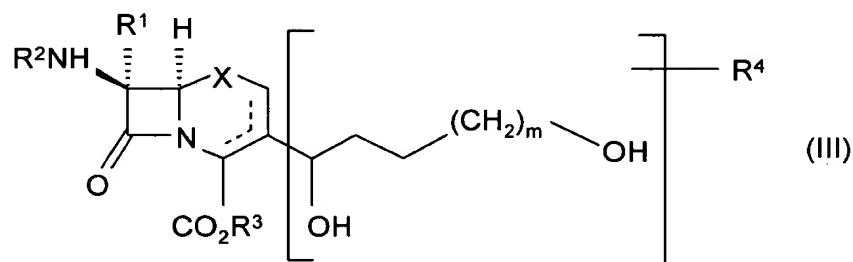


where R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and m are as defined in formulae (II) and (III) above, and the compound of formula 2-ephem (IIB) is then converted into a 3-ephem a compound of formula (IIA):



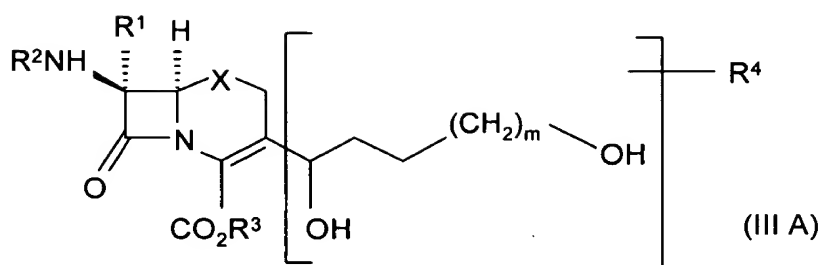
where  $R^1, R^2, R^3, R^4, X$  and  $m$  are as defined in formulae (II) and (III) above.

21. (PREVIOUSLY AMENDED) A compound of formula (III),

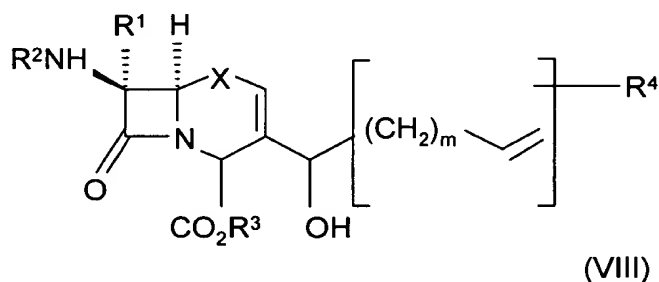


wherein  $R^1$  is hydrogen, methoxy or formamido;  $R^2$  is an acyl group;  $R^3$  is hydrogen or a carboxy protecting group;  $R^4$  represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, amino, alkylamino, acylamino, dialkylamino,  $CO_2R$ ,  $CONR_2$ ,  $SO_2NR_2$  (where  $R$  is hydrogen or  $C_{1-6}$  alkyl), aryl and heterocyclyl, which may be the same or different;  $X$  is S, SO,  $SO_2$ , O, or  $CH_2$ ; and  $m$  is 1 or 2; and the dotted line indicates that the compound may be a 2-cephem or a 3-cephem system, and where the substituent(s)  $R^4$  when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.

22. (PREVIOUSLY AMENDED) The compound according to claim 21, wherein the compound is a compound of formula (IIIA):



23. (CURRENTLY AMENDED) A compound of formula (VIII):



wherein R<sup>1</sup> is hydrogen, methoxy or formamido; R<sup>2</sup> is an acyl group; CO<sub>2</sub>R<sup>3</sup> is CO<sub>2</sub>H, a carboxylate salt or a carboxy group protected by benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula -N=CHR<sup>7</sup> where R<sup>7</sup> is aryl or heterocyclic, or an *in vivo* hydrolysable ester group; R<sup>4</sup> represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO<sub>2</sub>R, CONR<sub>2</sub>, SO<sub>2</sub>NR<sub>2</sub> (where R is hydrogen or C<sub>1-6</sub> alkyl), aryl and heterocyclyl, which may be the same or different; X is S, SO, SO<sub>2</sub>, O, or CH<sub>2</sub>; and m is 1 or 2; and the dotted line indicates that the compounds (II) and (III) may be a 2-cephem or a 3-cephem system, and where in formula (III) the substituent(s) R<sup>4</sup> when other than hydrogen may replace any of the hydrogen atoms bonded to carbon atoms in the side chain.

24. (NEW) The process according to claim 16 wherein group (X) is a tartrate boronate group wherein R<sup>a</sup> alkylcarboxylate, R<sup>b</sup> is hydrogen, R<sup>c</sup> is alkylcarboxylate and R<sup>d</sup> is hydrogen.